10 Formation of normal control subject data base

20 Patient Selection and screening

101 Patient Presents to a Clinic with Memory Complaints, Family History of Alzheimer's Disease, ApoE4 Positive or Related Reasons

102 Patient Presents to a Clinic with History of Substance Abuse, Concern over Possible Brain Damage or Related Reasons

103 Patient Presents to a Clinic with a History of Head Injury, Cognitive Complaints, Headaches, Blurry Vision or Related Reasons

104 Patient Presents to a Clinic with Family History of Parkinson's Disease, Movement Disorder or Related Reasons

110 Standard Clinical Evaluation Performed: Baseline Laboratory Tests; Computerized Tomography or Magnetic Resonance Imaging Performed to Investigate Potential Causes of Complaint; and Neuro-psychological Testing is Performed

115 Other Causes of Cognitive Decline Ruled Out (Neoplasm, Endocrine Imbalance, Infection, Nutritional Deficiency etc.

120 Patient is Referred to the PET Center for Evaluation of Cognitive Decline Index

FIG. 1 Normal Subject Controls and Patient Selection for Development of the Cognitive Decline Index

200 Patients are injected with 10 mCi of FDG through a peripheral intravenous line.

↓

205 Control subjects were injected with 5 mCi.

↓

210 Patient/Subject Scanned; Raw Brain Image Data Collected in 2D Mode, Septa in Place

↓

211 10 Minute Emission Scan is Obtained for Patient

↓

212 5 Minute Transmission Scan is Obtained for Patient

↓

213 20 Minute Emission Scan is Obtained for all Controls

↓

214 5 Minute Transmission Scan is Obtained for all Controls

↓

215 Ordered Subject Expectation Maximization (OSEM) Reconstruction

↓

220 Segmented Transmission Scan Attenuation Correction

↓

225 Addition of Z-axis filter

↓

FIG. 2a Derivation of the Processed Digital Brain Image

230 Images are then reformatted for clinical evaluation on the GE Advance Workstation (Sun™ Ultra 60), and a Copy Prepared for Export to the Research Workstation for Use with SPM

↓

235 Copy Prepared for Export to the Research Workstation for Use with SPM

↓

240 Scans Converted to Analyze 7.5™ (Analyze Direct, LENEXA KS) Format

↓

245 Images Are then further Processed and Analyzed with SPM99 (SPM, Friston et al, 1995a) and Implemented in Matlab

↓

250 Management of the Image Data is Achieved by Utilizing the Digital Imaging and Communication in Medicine (DICOM) Format

↓

260 Convert to Signed, 16-bit, "Byte-swapped" Image

↓

265 "Byte-swapping" Option Taken Depending on Workstation Type

↓

270 Image Transformed into Talairach Space

↓

280 Image Spatially Transformed using Gaussian Kernel

FIG. 2a (Cont'd) Derivation of the Processed Digital Brain Image

300 SPM Group Analysis: Patients Compared to Normal Controls

↓

310 Extrema in Changes in Metabolic Brain Activity Evaluated

↓

320 SPM(Z) Maps Created; Tables of Regional Maxima Compiled

↓

330 Convert to Normal Distribution Z-score

↓

340 Identification and Location of Clusters with Highest Significance Using Significance Thresholds Uncorrected for Multiple Comparisons

↓

350 Coordinates of Locations of Significant Interest Identified from SPM results listing all maxima greater than 8mm apart

↓

360 Specific Loci from this Analysis are Used as Centers for 3-D, 1 cm Diameter Spherical (VOIs)

↓

370 Identification of Specific Loci in Brain as Volumes of Interest (VOI) created with the Marsbar© plug-in (Bret et al, 2002) for SPM

↓

380 Intensity of Each of the Voxels within the Spherical VOI is Read and the Average is Obtained

↓

390 Weights (Set CDI_1) for each VOI are Calculated Based on the Frequency of Abnormality of the VOI Data from All the Study Patients as Compared to All Controls with Greater Weight Given to Increased Frequency as Determined by Intensity Range Overlap for each Volume of Interest Ratio

↓

FIG. 2b Derivation of Region Location and Identification of VOIs

391 Import VOI Data Into Spreadsheet

↓

392 Determine Intensity Range Overlap for each VOI Ratio

↓

393 Create Weights for each Intensity Extreme

↓

394 Create Weighted VOI Ratio

↓

395 Scale and Normalize Ratio

↓

400 Calculation of CDI:

$$CDI = C_x + [\ \sum_{j=1}^{n} V_j X_j / n\ ] / [\ \sum_{i=1}^{m} W_i Y_i / m\ ]$$

Where X_j denotes the j^{th} Increased Intensity Value;

V_j denotes the j^{th} Weight for the j^{th} Increased Intensity Value;

Y_i denotes the i^{th} Decreased Intensity Value; and

W_i denotes the i^{th} Weight for the i^{th} Decreased Intensity Value.

C_x is the correction factor used to normalize the dataset.

↓

410 Weights of Set CDI_1 are then used as a baseline for calculation of a second set of Weights (Set CDI_2) to calculate CDI_2. Set CDI_2 is calculated by iterative optimization of each weight to maximally separate the patient from the controls

FIG. 2b (Cont'd) Derivation of Region Location and Identification of VOIs

500 CDI is Compared to Established Normal Range of Values; Presence of Normality or Abnormality is Determined

↓

510 If CDI Reading is Negative, Patient Educated About the Clinical Course of Potential Illnesses and Signs to Watch out for; Potential Benefit of Preventative Measures such as Antioxidants, Brain Exercises, Beneficial Diet and Adequate Rest are Discussed

↓

520 If CDI Reading is Positive, Patient Educated about the Meaning of a Positive CDI Reading, Projected Clinical Course of Illness, Benefit of Medication, Potential Benefit of Preventative Measures such as Antioxidants, Brain Exercises, Beneficial Diet and Adequate Rest are Discussed

↓

530 Following either Step 620 or Step 630, Results are Given to Referring Physician and Patient Scheduled for Re-evaluation in one year.

↓

540 Patient Data is Stored in the Comprehensive Patient Database

FIG. 2c Patient Diagnosis and Clinical Recommendations

Fig. 2D Construction of the Neural Network Based CDI (CDInn)

600 Append the Neural Network Toolbox to the Matlab Path

↓

610 Type the command "nntool" at the Matlab command prompt to start the NN graphical user interface

↓

620 Configure an artificial neural network with the features and parameters:

Name: CDInn
Type: Feed-forward back-propagation
Input ranges: [-1 1; -1 1; -1 1; -1 1; -1 1; -1 1; -1 1; -1 1; -1 1;]
Training function: trainlm
Adaption learning function: Learndgm
Performance function: MSE
Layers: 2
Number of neurons: 2
Transfer function neuron 1: purelin
Transfer function neuron 2: tansig

↓

630 VOI regions obtained from the specified locations:

Regions of increased activity:

vermis,
motor,
R pons, and
cerebellar nuclei

Regions of decreased activity:

posterior cingulate,
L parietal,
R parietal,
L temporal01, and
L temporal02

↓

640 Intensity data from the above regions are entered into the NN in the order:

vermis,
motor,
R pons,
cerebellar nuclei,
posterior cingulate,
L parietal,
L temporal01,
L temporal02,
R parietal.

↓

650 VOI Data are mean-normalized by subject, i.e. divided by the average of the 9 regions measured for each subject. This gave each subjects data set a mean value =1.

↓

660 The datasets are next divided into comparably sized subgroups (c1 denotes control subgroup # 1, p1 = patient subgroup #1, etc): [c1=16, c2=17, p1=16, p2=16].

↓

670 Four mixed groups were made from these by pairing controls with patients to give: [c1p1, c1p2, c2p1, c2p2].

680 These datasets are then exported (from Excel) to a text file, subsequently imported into Matlab and converted to a .mat file for use by Matlab.

690 Rescaling is performed to ensure the input range is appropriately matched for the tansig function on the output layer of the NN, which will classify the input data in the range ± 1. This is carried out in the main Matlab window at the command prompt. As an example, the dataset c1p1 is rescaled using the premnmx function:

[c1p1_rescale,minp,maxp]=premnmx(c1p1)

700 The rescaled output from this function is labeled and saved as **c1p1_rescale.mat.** This is done for each of the four paired datasets listed above.

710 These four files are then used as "inputs" for neural net training. For training of the neural net, each input file had a "target" file to which the neural network tried to match the input dataset to. These files were labeled to match the dataset from which they were used, thus for **c1p1_rescale.mat**, the "target" file was labeled **c1p1t.mat**. Each target file consisted of a single row of digits with the same number of columns as the input file. For each patient (column) in the c1p1_rescale dataset, a "-1" was present in the c1p1t.mat file, and for each control, a "1" was assigned. Thus, the four input and target datasets were:

Input	Target
c1p1_rescale.mat	**c1p1t.mat**
c1p2_rescale.mat	**c1p2t.mat**
c2p1_rescale.mat	**c2p1t.mat**
c2p2_rescale.mat	**c2p2t.mat**

720 The network is then trained on each input dataset

730 The resulting trained CDInn is tested on the full dataset to assess its classification accuracy.

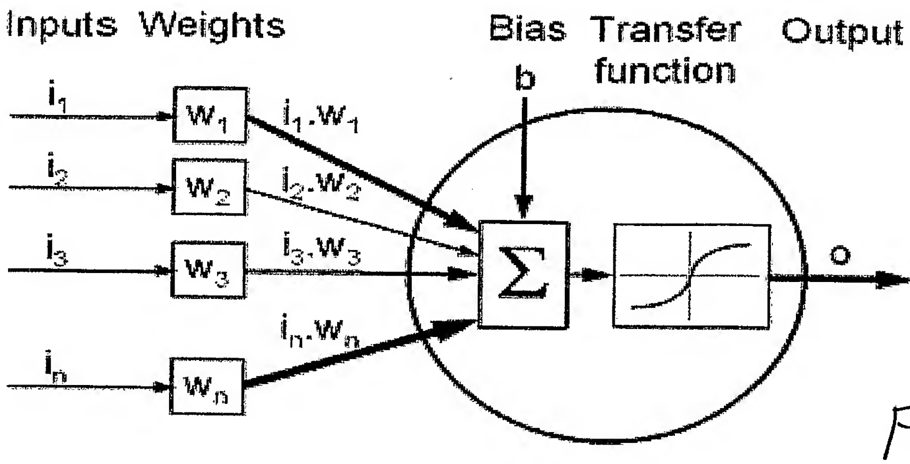


FIG. 13

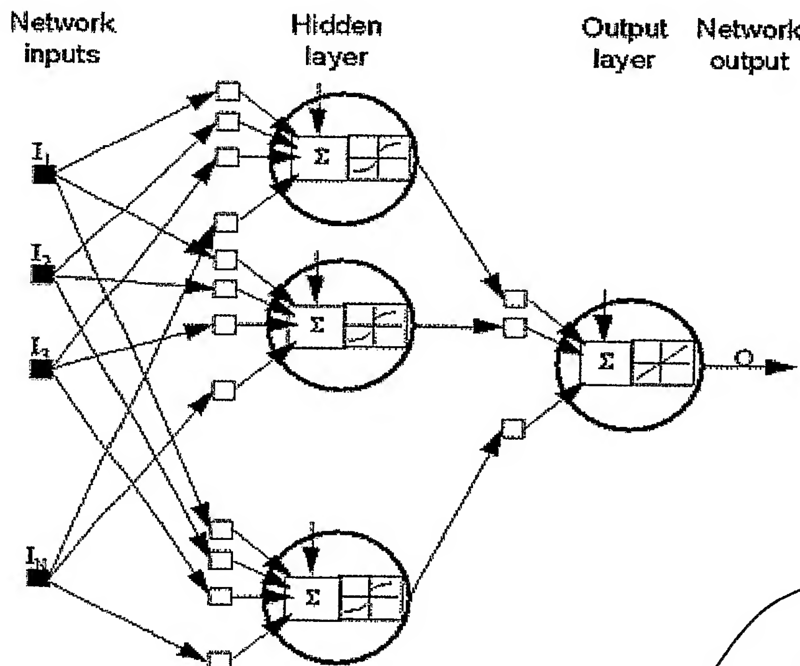
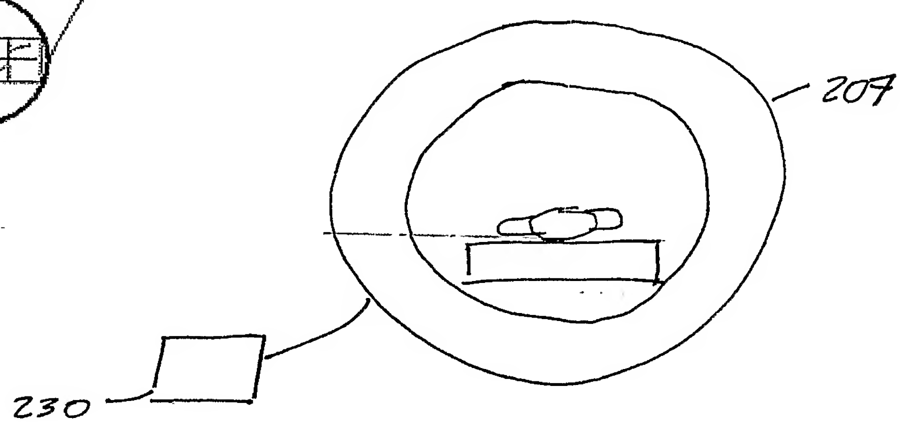


FIG. 14

FIG. 3A



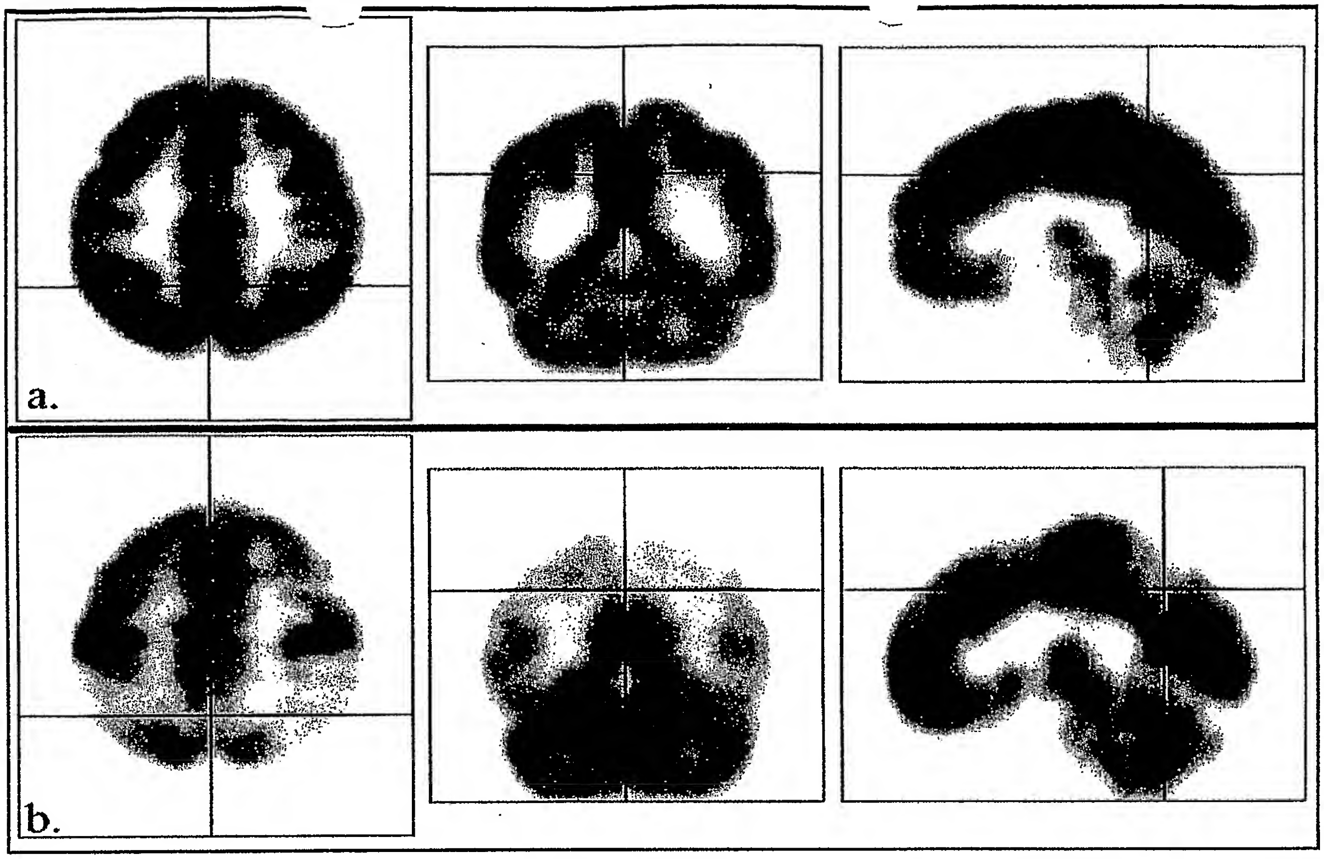
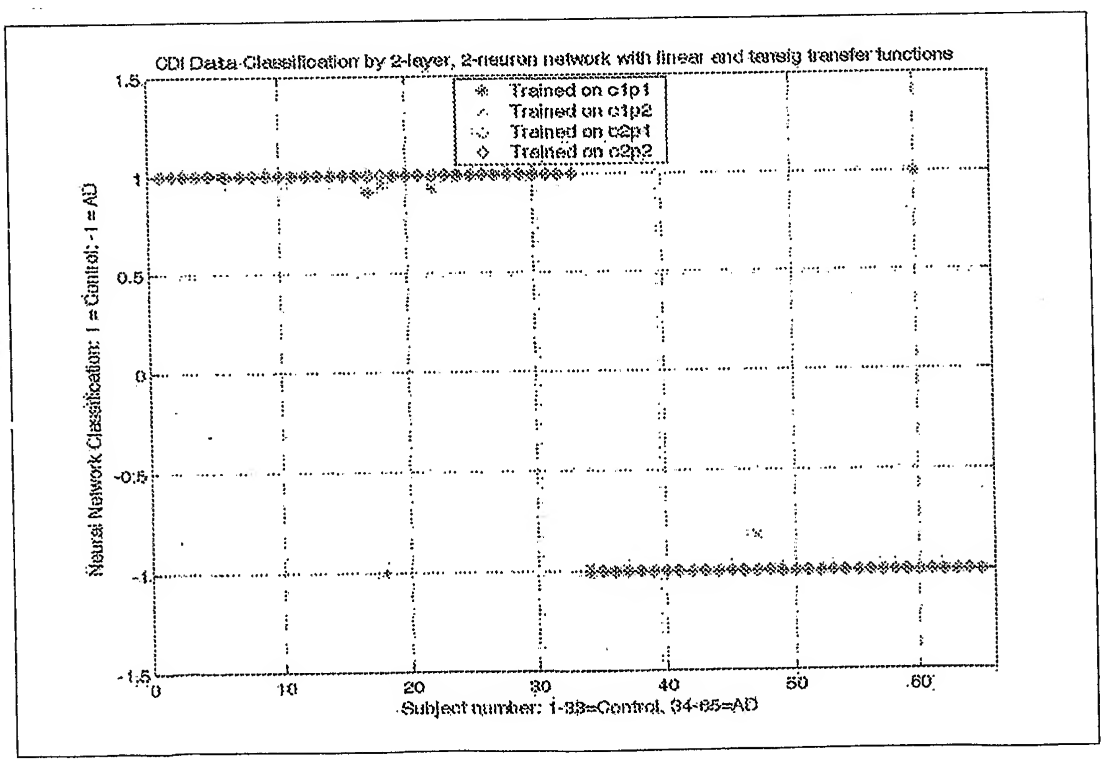
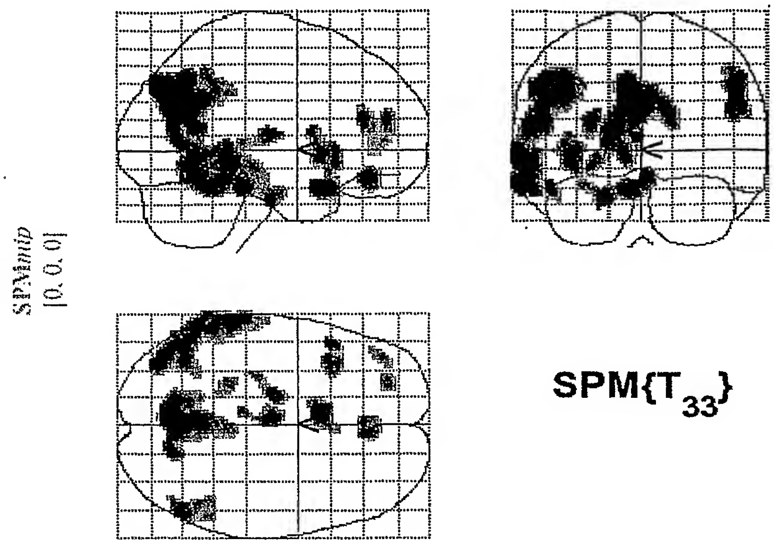

a.
b.

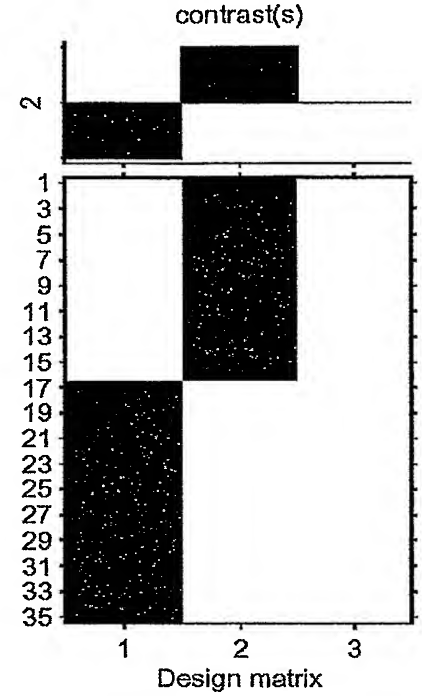
Fig. 3B

FIG. 16


CDI Data Classification by 2-layer, 2-neuron network with linear and tansig transfer functions
Trained on c1p1
Trained on c1p2
Trained on c2p1
Trained on c2p2
Neural Network Classification: 1 = Control; -1 = AD
Subject number: 1-33=Control, 34-65=AD
1.5
1
0.5
0
-0.5
-1
-1.5
0
10
20
30
40
50
60



SPM{T_{33}}



SPMresults: Results_122802_MCIvsOldctrls
Height threshold T = 2.50
Extent threshold k = 50 voxels

Statistics: *volume summary (p−values corrected for entire volume)*

set-level		cluster-level			voxel-level				x,y,z {mm}
p	c	$p_{corrected}$	k_E	$p_{uncorrected}$	$p_{corrected}$	T	$(Z_{\equiv})$	$p_{uncorrected}$	
0.173	14	0.000	1945	0.000	0.106	5.29	(4.47)	0.000	-4 -70 30
					0.483	4.54	(3.97)	0.000	-14 -68 16
					0.616	4.37	(3.86)	0.000	-4 -58 28
		0.000	2610	0.000	0.788	4.16	(3.70)	0.000	-42 -74 36
					0.804	4.13	(3.68)	0.000	-56 -56 16
					0.881	4.01	(3.59)	0.000	-60 -56 -8
		0.862	202	0.064	0.883	4.01	(3.59)	0.000	-6 14 -24
		0.247	450	0.009	0.951	3.84	(3.47)	0.000	52 -64 38
					1.000	2.96	(2.77)	0.003	54 -50 44
		1.000	58	0.302	0.998	3.49	(3.20)	0.001	-48 18 -22
		0.991	114	0.153	0.998	3.48	(3.19)	0.001	-4 -12 10
					1.000	2.81	(2.64)	0.004	-8 -30 4
		0.996	101	0.177	0.999	3.43	(3.15)	0.001	4 38 -16
		0.944	162	0.093	1.000	3.37	(3.10)	0.001	-10 14 -2
					1.000	2.90	(2.71)	0.003	-12 8 12
		0.981	131	0.127	1.000	3.32	(3.07)	0.001	-20 -14 -28
					1.000	2.91	(2.72)	0.003	-30 -22 -20
		0.888	191	0.071	1.000	3.22	(2.98)	0.001	-38 20 -2
		0.997	95	0.189	1.000	3.21	(2.97)	0.001	-26 48 16
		0.993	110	0.160	1.000	3.05	(2.84)	0.002	-2 36 18
					1.000	2.69	(2.54)	0.006	-2 42 2
		1.000	69	0.261	1.000	3.00	(2.80)	0.003	-24 -38 -6
		1.000	50	0.338	1.000	2.93	(2.74)	0.003	-40 46 6

table shows at most local maxima > 8.0mm apart per cluster

Height threshold: T = 2.50, p = 0.009 (1.000 corrected)
Extent threshold: k = 50 voxels, p = 0.338 (1.000 corrected)
Expected voxels per cluster, <k> = 58.849
Expected number of clusters, <c> = 10.48

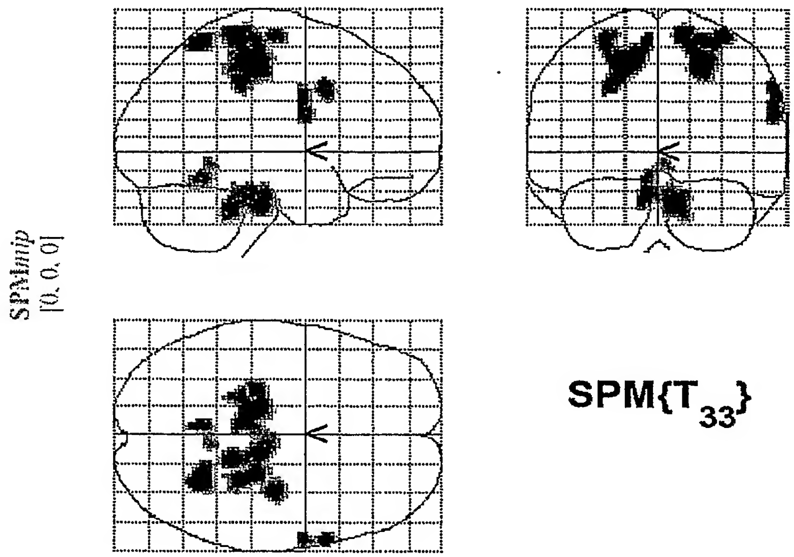
Degrees of freedom = [1.0, 33.0]
Smoothness FWHM = 13.5 13.7 16.0 {mm} = 6.7 6.9 8.0 {voxels}
Search volume: S = 1815544 mm^3 = 226943 voxels = 559.8 resels
Voxel size: [2.0, 2.0, 2.0] mm (1 resel = 370.95 voxels)

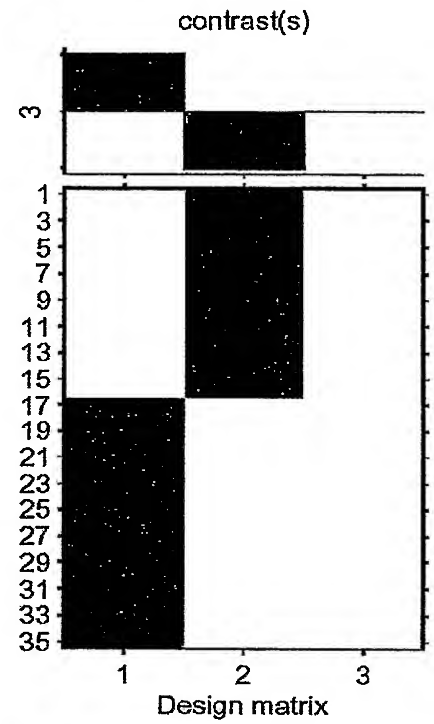
Statistics: *single cluster summary (p−values corrected for entire volume)*

cluster-level			voxel-level				x,y,z {mm}
$p_{corrected}$	k_E	$p_{uncorrected}$	$p_{corrected}$	T	$(Z_{\equiv})$	$p_{uncorrected}$	
0.000	2610	0.000	0.788	4.16	(3.70)	0.000	-42 -74 36
			0.804	4.13	(3.68)	0.000	-56 -56 16
			0.881	4.01	(3.59)	0.000	-60 -56 -8
			0.892	3.99	(3.58)	0.000	-62 -36 -6
			0.905	3.96	(3.56)	0.000	-64 -30 -22
			0.938	3.89	(3.50)	0.000	-58 -46 -22
			0.977	3.74	(3.39)	0.000	-50 -60 42
			0.987	3.66	(3.33)	0.000	-42 -62 44
			0.998	3.50	(3.21)	0.001	-52 -62 28
			1.000	3.03	(2.83)	0.002	-56 -46 36
			1.000	3.01	(2.81)	0.002	-54 -68 16
			1.000	2.99	(2.79)	0.003	-62 -24 -8
			1.000	2.83	(2.66)	0.004	-62 -18 -24
			1.000	2.76	(2.60)	0.005	-32 -56 40

FIG. 4

Increases in MCI





SPMresults: \results_122802_MCIvsOldctrls
Height threshold T = 3.00
Extent threshold k = 100 voxels

Statistics: *volume summary (p-values corrected for entire volume)*

set-level		cluster-level			voxel-level				x,y,z {mm}
p	c	$p_{corrected}$	k_E	$p_{uncorrected}$	$p_{corrected}$	T	$(Z_{\equiv})$	$p_{uncorrected}$	
0.003	6	0.002	745	0.000	0.027	5.86	(4.82)	0.000	-16 -24 52
					0.528	4.48	(3.93)	0.000	-26 -26 66
					0.773	4.18	(3.71)	0.000	-6 -34 62
		0.318	188	0.026	0.120	5.23	(4.43)	0.000	26 -54 64
		0.003	678	0.000	0.202	5.00	(4.28)	0.000	10 -22 -30
					0.622	4.37	(3.85)	0.000	14 -38 -34
					0.925	3.92	(3.52)	0.000	-6 -28 -24
		0.001	873	0.000	0.379	4.68	(4.07)	0.000	34 -16 68
					0.434	4.60	(4.02)	0.000	26 -32 52
					0.596	4.40	(3.87)	0.000	14 -38 68
		0.530	138	0.051	0.837	4.08	(3.65)	0.000	62 12 36
					0.937	3.89	(3.50)	0.000	62 0 22
					0.994	3.59	(3.28)	0.001	62 0 34
		0.683	110	0.077	0.995	3.57	(3.26)	0.001	-6 -54 -16
					1.000	3.30	(3.05)	0.001	4 -50 -6

table shows at most local maxima > 8.0mm apart per cluster

Height threshold: T = 3.00, p = 0.003 (1.000 corrected)
Extent threshold: k = 100 voxels, p = 0.090 (0.739 corrected)
Expected voxels per cluster, <k> = 35.683
Expected number of clusters, <c> = 1.34

Degrees of freedom = [1.0, 33.0]
Smoothness FWHM = 13.5 13.7 16.0 {mm} = 6.7 6.9 8.0 {voxels}
Search volume: S = 1815544 mm^3 = 226943 voxels = 559.8 resels
Voxel size: [2.0, 2.0, 2.0] mm (1 resel = 370.95 voxels)

Fig. 5

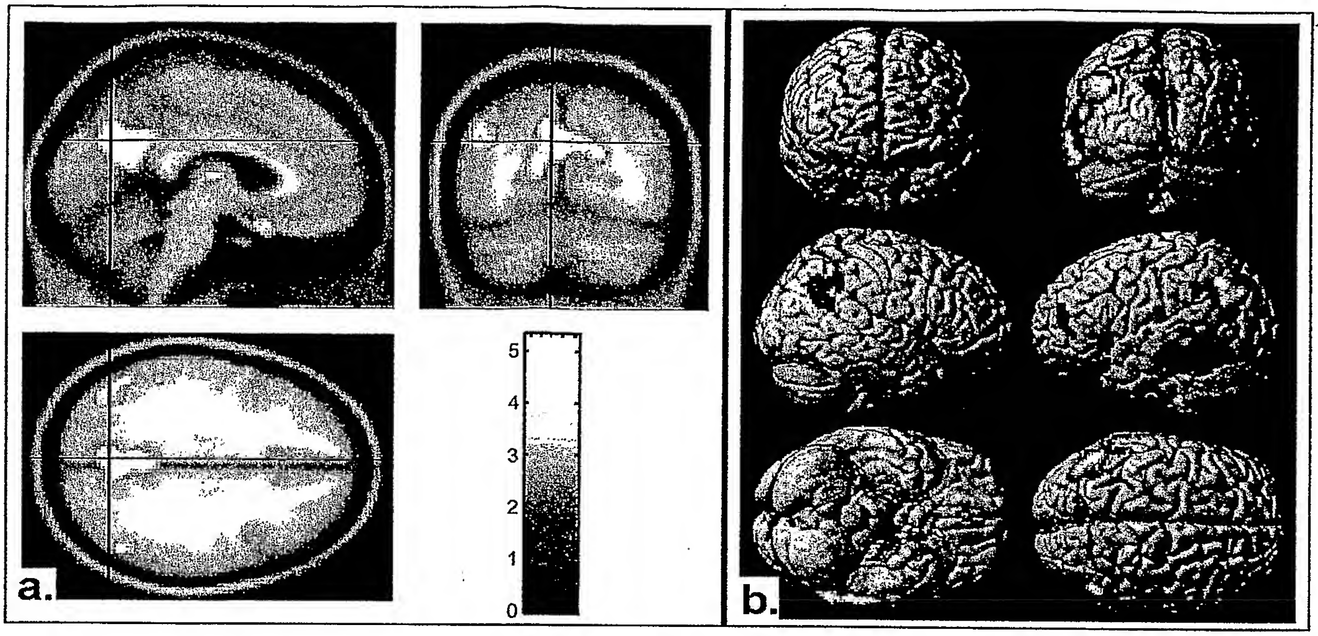


Fig. 6

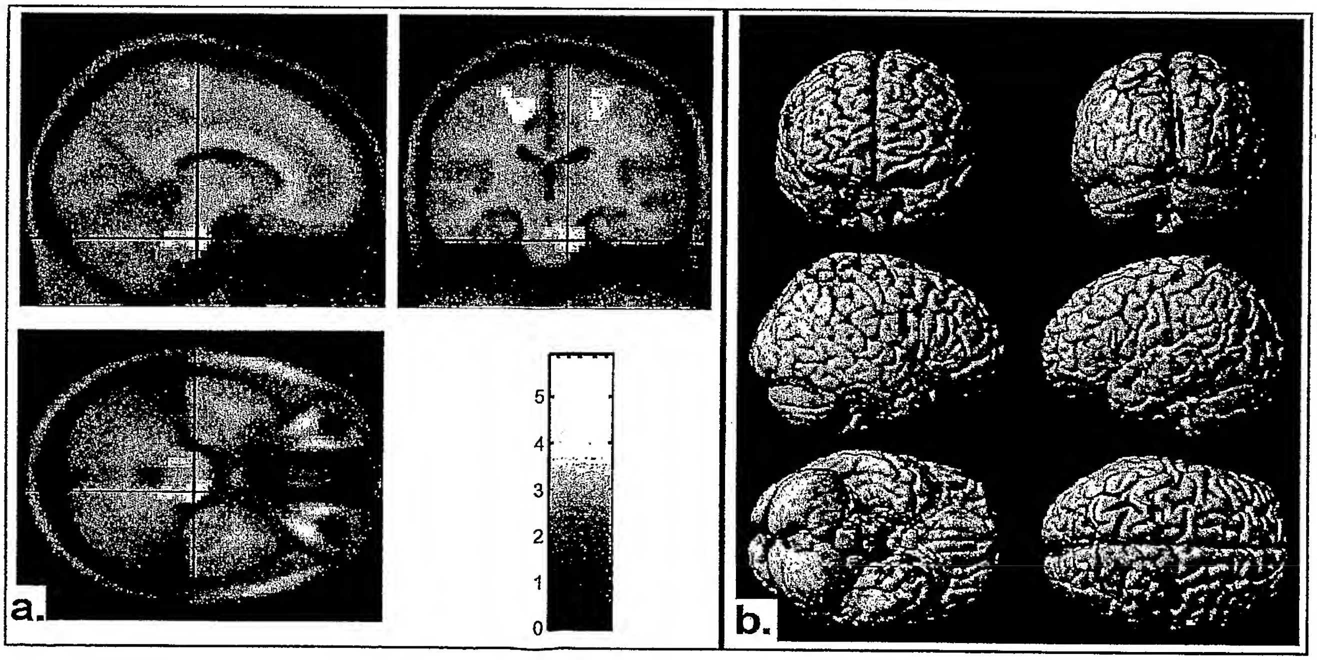


Fig. 7

Fig. 8

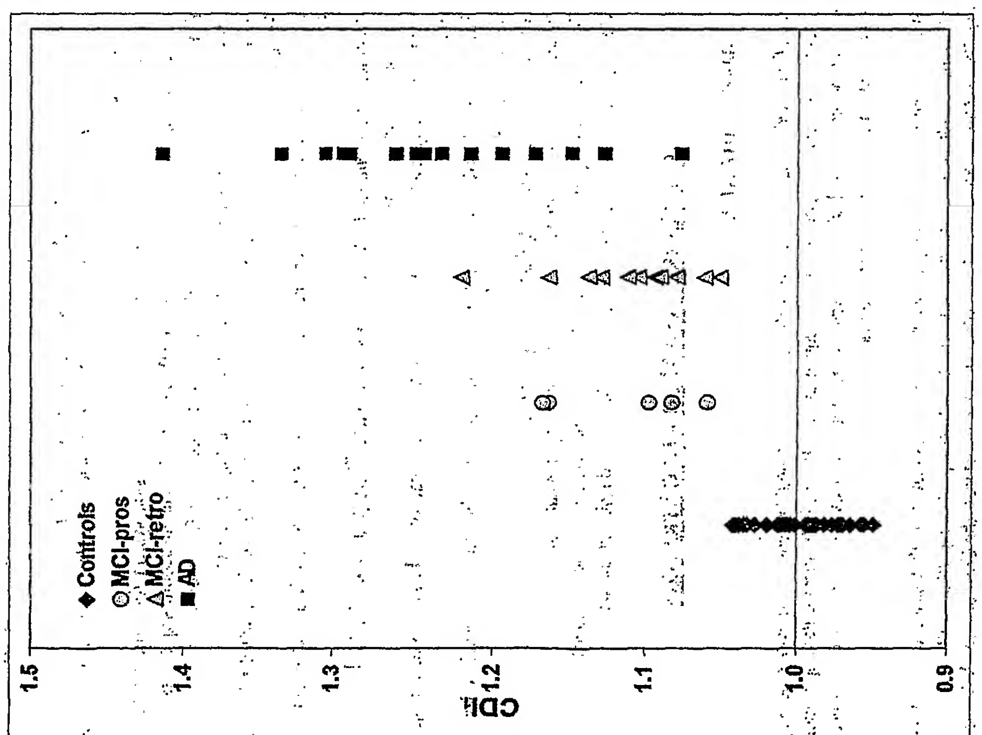

Controls
MCI-pros
MCI-retro
AD
CDIF
1.5
1.4
1.3
1.2
1.1
1.0
0.9

FIG. 9

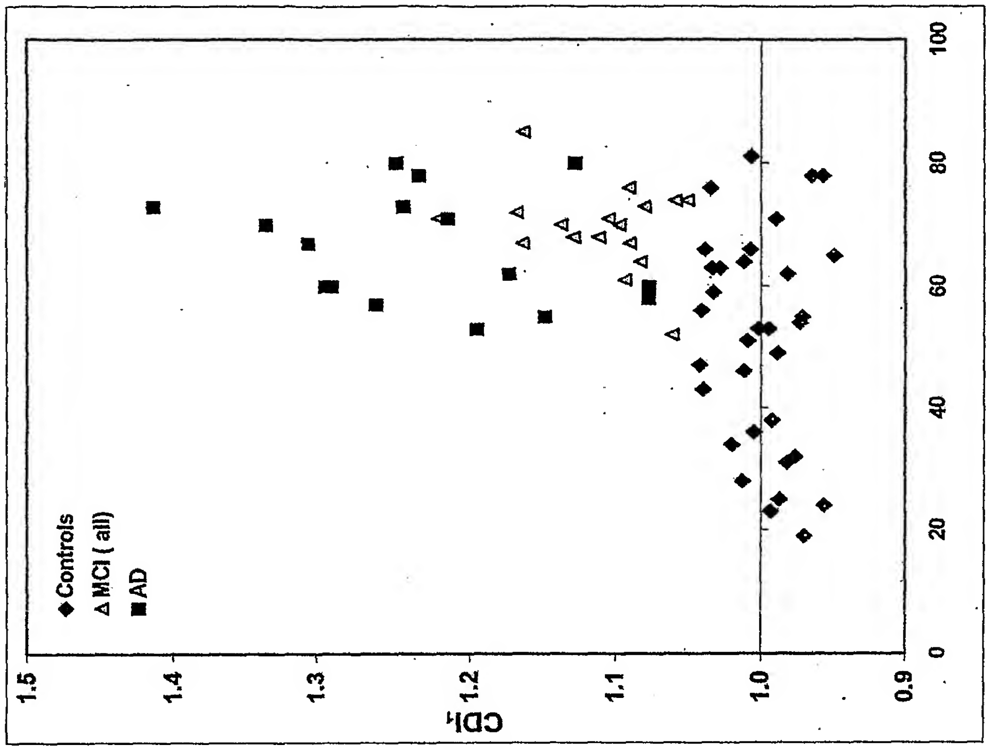

Controls
MCI (all)
AD
CDIF
1.5
1.4
1.3
1.2
1.1
1.0
0.9
0
20
40
60
80
100

FIG. 10

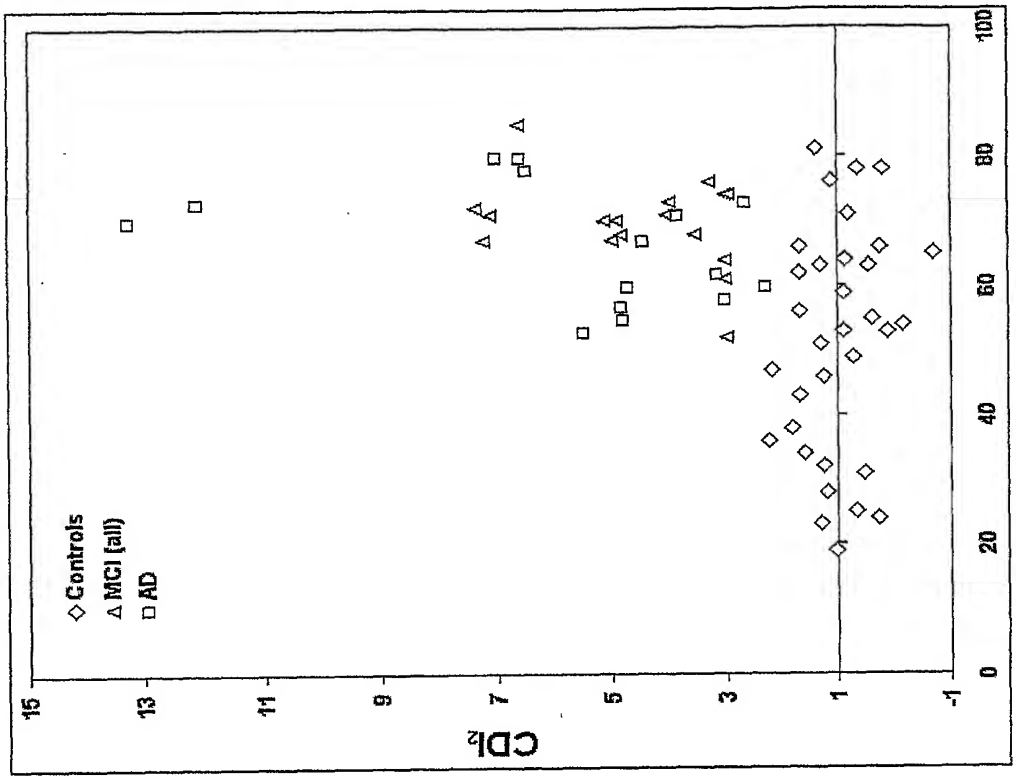

Controls
MCI (all)
AD
CDI_2
15
13
11
9
7
5
3
1
-1
0
20
40
60
80
100

FIG. 12

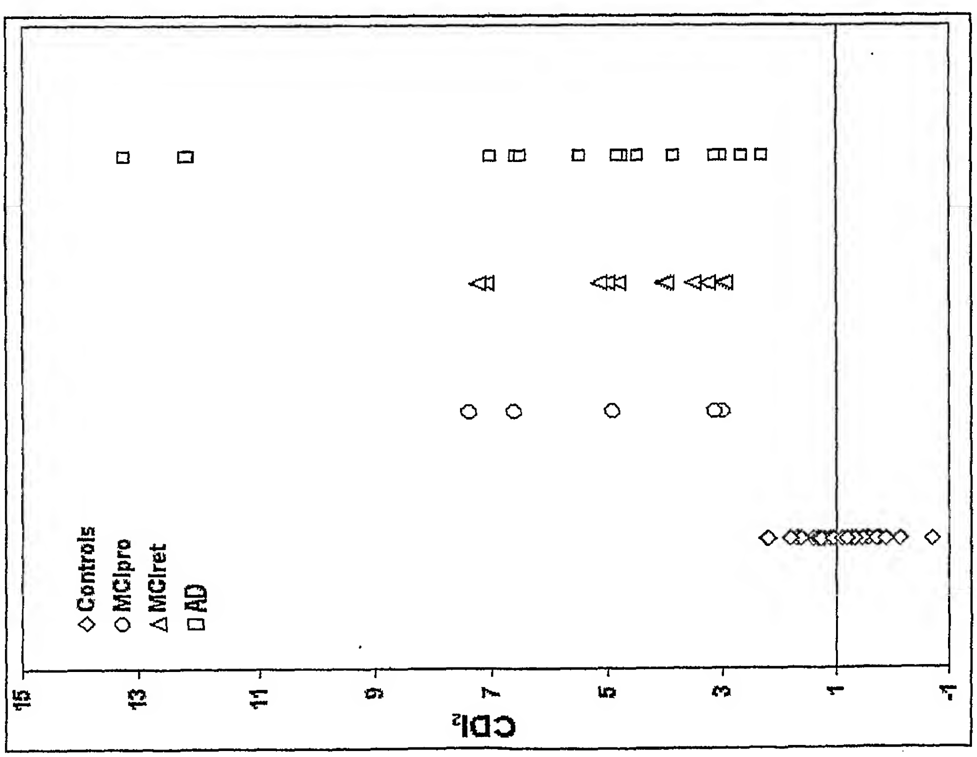

Controls
MCIpro
MCIret
AD
CDI_2
15
13
11
9
7
5
3
1
-1

FIG. 11

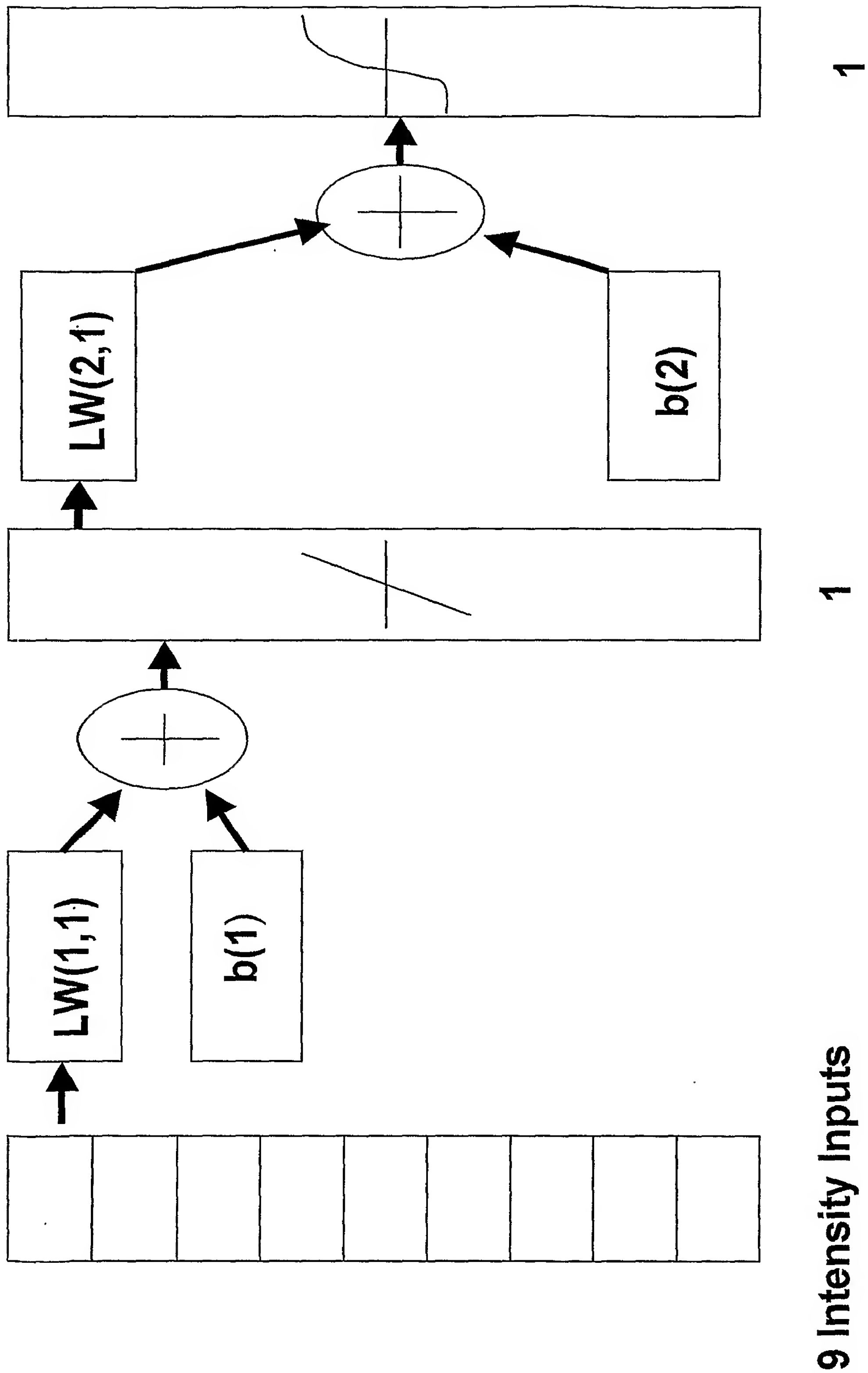


FIG. 15